IMMUNOBIOLOGY

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

THIRD EDITION

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Inherited immunodeficiency diseases.

Immunodeficiencies occur when one or more components of the immune system is defective. The commonest cause of immune deficiency worldwide is malnutrition; however, in developed countries, most immunodeficiency diseases are inherited, and these are usually seen in the clinic as recurrent or overwhelming infections in very young children. Less commonly acquired immunodeficiencies with causes other than malnutrition can manifest later in life. While the pathogenesis of many of these acquired disorders has remained obscure, some are caused by known agents, such as drugs or irradiation which damage lymphocytes, or infection with HIV. By examining which infections accompany a particular inherited or acquired immunodeficiency, we can see which components of the immune system are important in the response to particular infectious agents. The inherited immunodeficiency diseases also reveal how interactions between different cell types contribute to the immune response and to the developmental sequence of T and B lymphocytes. Finally, these diseases can lead us to the defective gene, often revealing new information about the molecular basis of immune processes and providing the necessary information for diagnosis, genetic counseling, and gene therapy.

10-6 Inherited immunodeficiency diseases are caused by recessive gene defects.

Before the advent of antibiotic therapy, it is likely that most individuals with inherited immune defects died in infancy or early childhood because of their susceptibility to particular classes of pathogens (Fig. 10.8). Such deaths would not have been easy to identify, since many normal infants also died of infection. Thus, the first immunodeficiency disease was not described until 1952; since that time many inherited immunodeficiency diseases have been identified. Most of the gene defects that cause these inherited immunodeficiencies are recessive, and for this reason, many common immunodeficiencies are caused by mutations of genes on the X chromosome. Recessive defects cause disease only when both chromosomes are defective. As males have only one X chromosome, however, all males who inherit an X chromosome carrying a defective gene will manifest disease, whereas female carriers, having two X chromosomes, are perfectly healthy. Immunodeficiency diseases that affect many steps in B- and T-lymphocyte development have been described, as have defects in surface molecules that are important for T- or B-cell function. Defects in phagocytic cells, in complement, in cytokines, in cytokine receptors, and in molecules that mediate effector responses also occur (see Fig. 10.8). Thus immunodeficiency may be caused by defects either in the adaptive or the innate immune system. Individual examples of these diseases will be described in later sections.

More recently, the use of gene knock-out techniques in mice has allowed the creation of many immunodeficient states that are adding rapidly to our knowledge of the contribution of individual molecules to normal immune function. Nevertheless, human immunodeficiency disease is still the best source of insight into host defense in humans. The study of immunodeficiency provides the clearest evidence of the normal pathways of host defense against infectious disease. For example, as we will see later, deficiency in antibody, complement, or phagocytic function

Fig. 10.8 Human immunodeficiency syndromes. The specific gene defect, the consequence for the immune system, and the resulting disease susceptibilities are listed for some common and some rare human immunodeficiency syndromes. ADA, adenosine deaminase; PNP, purine nucleotide phosphorylase; TAP, transporters associated with antigen processing; WASP, Wiskott-Aldrich syndrome protein; EBV, Epstein-Barr virus; NK, natural killer.

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	ADA deficiency	No T or B cells	General
	PNP deficiency	No T or B cells	General
	X-linked *scid*. γ_c chain deficiency	No T cells	General
	Autosomal *scid* DNA repair defect	No T or B cells	General
DiGeorge syndrome	Thymic aplasia	Variable numbers of T and B cells	General
MHC class I deficiency	TAP mutations	No CD8 T cells	Viruses
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General
Wiskott-Aldrich syndrome	X-linked: defective WASP gene	Defective polysaccharide antibody responses	Encapsulated extracellular bacteria
Common variable immunodeficiency	Unknown: MHC-linked	Defective antibody production	Extracellular bacteria
X-linked agamma-globulinemia	Loss of Btk tyrosine kinase	No B cells	Extracellular bacteria, viruses
X-linked hyper-IgM syndrome	Defective CD40 ligand	No isotype switching	Extracellular bacteria
Selective IgA and/or IgG deficiency	Unknown: MHC-linked	No IgA synthesis	Respiratory infections
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.
Natural killer (NK) cell defect	Unknown	Loss of NK function	Herpes viruses
X-linked lympho-proliferative syndrome	Unknown: X-linked	EBV-triggered immunodeficiency	EBV
Ataxia telangiectasia	Gene with PI-3 kinase homology	T cells reduced	Respiratory infections
Autoimmune lympho-proliferative disease	Mutant Fas	Failure of T- and B-cell apoptosis	Autoimmune disorders

each increases the risk of infection by certain pyogenic bacteria. This shows that the normal pathway of host defense against such bacteria is binding of antibody followed by fixation of complement, which allows uptake of opsonized bacteria by phagocytic cells. Breaking any one of the links in this chain of events leading to bacterial killing causes a similar immunodeficient state.

The study of immunodeficiency also teaches us about the redundancy of mechanisms of host defense against infectious disease. The first two humans to be discovered with hereditary deficiency of complement were healthy immunologists. This teaches us two lessons. The first is that there are multiple protective immune mechanisms against infection; for example, while there is abundant evidence that complement deficiency increases susceptibility to pyogenic infection, not every human with complement deficiency suffers from recurrent infections. The second lesson is about the phenomenon of **ascertainment artefact**. When an unusual observation is made in a patient with disease, there is a temptation to seek a causal link. However, no one would suggest that complement deficiency causes a genetic predisposition to becoming an immunologist. Complement deficiency was discovered in immunologists because they used their own blood in their experiments. If a particular measurement is only made in a group of patients with a particular disease, it is inevitable that the only abnormal results will be discovered in patients with that disease. This is an ascertainment artefact and emphasizes the importance of studying appropriate controls.

10-7 The main effect of low levels of antibody is an inability to clear extracellular bacteria.

Pyogenic or pus-forming bacteria have polysaccharide capsules which make them resistant to phagocytosis. Normal individuals can clear infections by such bacteria because antibody and complement opsonize the bacteria, making it possible for phagocytes to ingest and destroy them. The principal effect of deficiencies in antibody production is therefore failure to control this class of bacterial infection, although susceptibility to some viral infections, most notably those caused by enteroviruses, is also increased because of the importance of antibodies in neutralizing infectious viruses that enter the body through the gut (see Chapter 8).

The first description of an immunodeficiency disease was Ogden C. Bruton's account, in 1952, of the failure of a male child to produce antibody. As this defect is inherited in an X-linked fashion and is characterized by the absence of immunoglobulin in the serum, it was called **Bruton's X-linked agammaglobulinemia (XLA)**. The absence of antibody can be detected using electrophoresis (see Section 2-9). Since then, many more diseases of antibody production have been described, most of them the consequence of failures in the development or activation of B lymphocytes.

The defective gene in XLA is now known to encode a protein tyrosine kinase known as Btk (Bruton's tyrosine kinase). This protein is expressed in polymorphonuclear neutrophilic leukocytes as well as in B cells, although only B cells are defective in these patients, in whom B-cell maturation halts at the pre-B-cell stage. Thus it is likely that Btk is required to couple the pre-B-cell receptor (which consists of heavy chains, surrogate light chains, and Igα and Igβ) to nuclear events that lead to pre-B-cell growth and differentiation. A homologous kinase called Itk has been found in T cells and is required for normal T-cell development. Defects in Btk are analogous to defects in Lck in T-cell development (see Section 6-8). In the mouse, Lck deficiency leads to the arrest of thymocyte development at the double-negative stage, after T-cell receptor β-chain gene rearrangement and cell-surface expression but before the rearrangement of the α-chain genes. Thus, there may be a cascade of tyrosine kinases, involving Lck and Itk in double-negative thymocytes, and Blk and Btk in pre-B cells, that is important for lymphocyte development. In both Lck and Btk deficiencies,

some B or T cells mature despite the defect in the signaling molecule, suggesting that signals transmitted by these kinases promote rearrangement of light-chain or α-chain genes, respectively, but are not absolutely required.

Since the gene responsible for XLA is found on the X chromosome, it is possible to identify female carriers by analyzing X-chromosome inactivation in their B cells. During development, female cells randomly inactivate one of their two X chromosomes. Since the product of a normal *btk* gene is required for normal B-lymphocyte development, only cells in which the X chromosome carrying the normal allele of *btk* is active can develop into mature B cells (with a very few exceptions, see earlier). Thus, in female carriers of mutant *btk* genes, almost all B cells have the normal X chromosome as the active X. By contrast, the active X chromosomes in the T cells and macrophages of carriers are equally distributed between normal and *btk* mutants. This fact allowed female carriers of XLA to be identified even before the nature of *btk* was known. Non-random X inactivation only in B cells also demonstrates conclusively that the *btk* gene is required for normal B-cell development but not for the development of other cell types, and that Btk must act within B cells rather than on stromal cells or other cells required for B-cell development (Fig. 10.9).

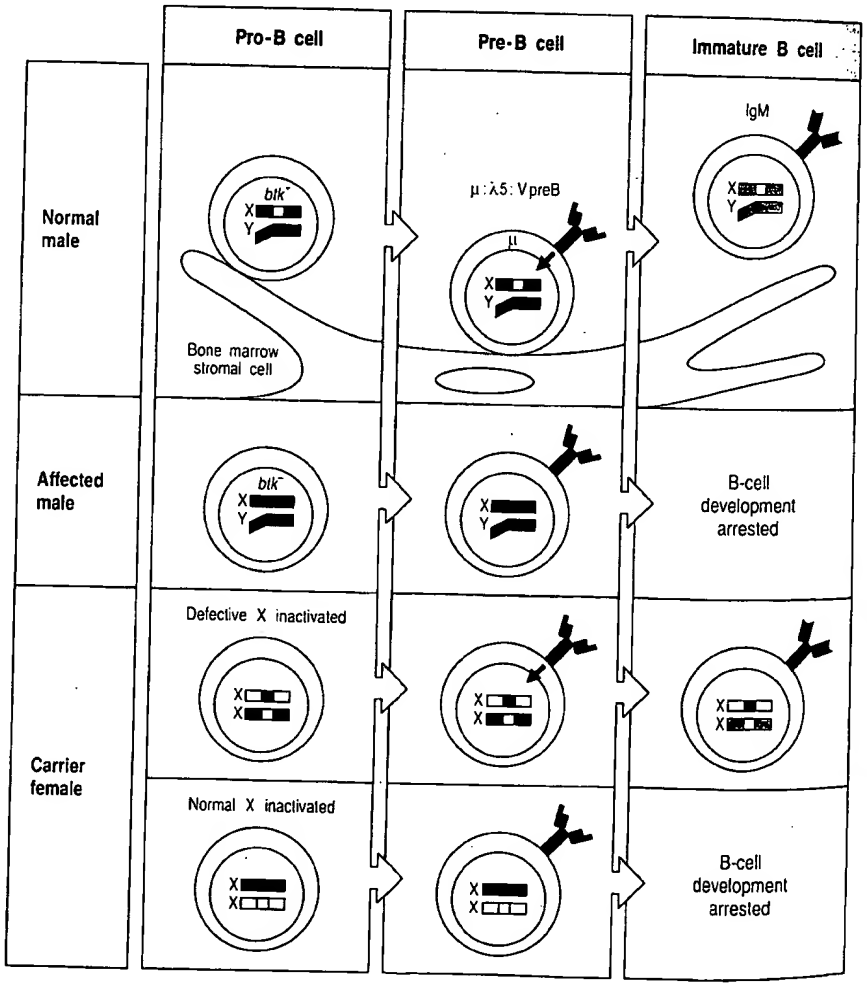

Fig. 10.9 The product of the *btk* gene is important for B-cell development. In X-linked agammaglobulinemia (XLA), a protein tyrosine kinase called Btk, encoded on the X chromosome, is defective. In normal individuals, B-cell development proceeds through a stage in which the pre-B cell receptor consisting of μ:λ5:Vpre-B transduces a signal via Btk, triggering further B-cell development. In males with XLA, no signal can be transduced and although the pre-B-cell receptor is expressed, the B cells develop no further. In female mammals, including humans, one of the two X chromosomes in each cell is permanently inactivated early in development. Since the choice of which chromosome to inactivate is random, half of the pre-B cells in a carrier female express a wild-type *btk*, while half express the defective gene. None of the B cells that express *btk* from the defective chromosome can develop into mature B cells. Therefore, in the carrier, mature B cells always have the non-defective X chromosome active. This is in sharp contrast to all other cell types, which express the non-defective chromosome in only half of the population. Non-random X chromosome inactivation in a particular cell lineage is a clear indication that the product of the X-linked gene is required for the development of cells of that lineage. It is also sometimes possible to identify the stage at which the gene product is required, by detecting the point in development at which X-chromosome inactivation develops bias. Using this kind of analysis, one can identify carriers of X-linked traits such as XLA without needing to know the nature of the mutant gene.

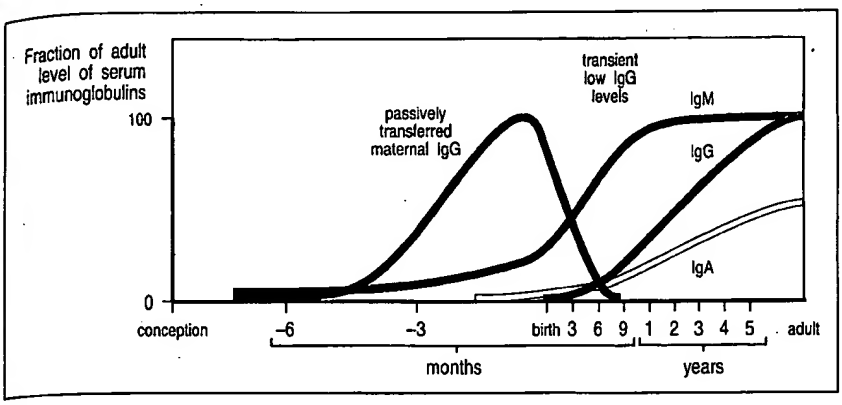

Fig. 10.10 Immunoglobulin levels in newborn infants fall to low levels around 6 months of age. Newborn babies have high levels of IgG, transported across the placenta from the mother during gestation. After birth, production of IgM starts almost immediately; production of IgG, however, does not begin for about 6 months, during which time the total level of IgG falls as the maternally acquired IgG is catabolized. Thus IgG levels are low from about the age of 3 months to 1 year, which may lead to susceptibility to disease. IgG levels fall further for longer in premature infants, resulting in a higher rate of infection because, at the time of birth, the level of transferred maternal IgG is lower and as the premature infant's immune system is less developed at birth, antibody production by the infant occurs at a later time after birth.

The commonest humoral immune defect is the transient deficiency in immunoglobulin production that occurs in the first 6–12 months of life. The newborn infant has initial antibody levels comparable with those of the mother, because of the transplacental transport of maternal IgG (see Chapter 8). As the transferred IgG is catabolized, antibody levels gradually decrease until the infant begins to produce useful amounts of its own IgG at about 6 months of age (Fig. 10.10). Thus, IgG levels are quite low between the ages of 3 months and 1 year and active IgG antibody responses are poor. In some infants, this can lead to a period of heightened susceptibility to infection. This is especially true for premature babies, who begin with lower levels of maternal IgG and also reach immune competence longer after birth.

The most common inherited form of immunoglobulin deficiency is selective IgA deficiency, which is seen in about 1 person in 800. Although no obvious disease susceptibility is associated with selective IgA defects, they are commoner in people with chronic lung disease than in the general population. This suggests that lack of IgA may result in a predisposition to lung infections with various pathogens and is consistent with the role of IgA in defense at the body's surfaces. The genetic basis of this defect is unknown but some data suggest that a gene of unidentified function mapping in the class III region of the MHC may be involved. A related syndrome called common variable immunodeficiency, in which there is generally a deficiency in IgG and IgA, also maps to the MHC region.

Low levels of antibody production lead to a susceptibility to infection with a fairly specific set of pathogens. People with pure B-cell defects resist many pathogens successfully. They cannot control infection with extracellular bacteria but these infections can be suppressed with antibiotics and periodic infusions with human immunoglobulin collected from a large pool of donors. Since there are antibodies to most pathogens in the immunoglobulin pool, it serves as a fairly successful shield against infection.

10-8 T-cell defects can result in low antibody levels.

Patients with **X-linked hyper-IgM syndrome** have normal B- and T-cell development and high serum levels of IgM but make very limited IgM antibody responses against T-cell dependent antigens and produce immunoglobulin isotypes other than IgM and IgD only in trace amounts. This makes them susceptible to infection with extracellular bacteria and certain opportunistic organisms such as *Pneumocystis carinii*. The molecular defect in this disease is in the CD40 ligand on activated T cells,

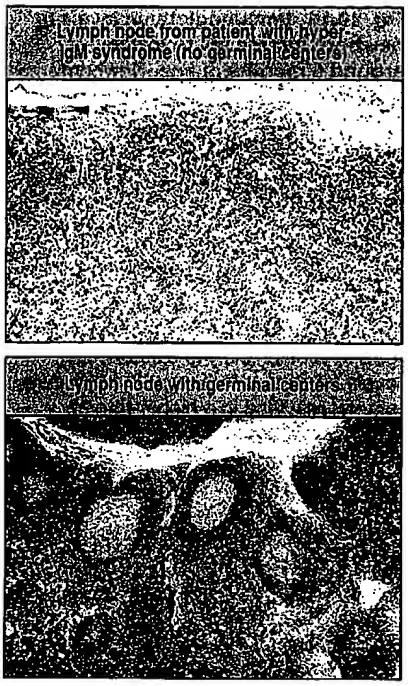

Fig. 10.11 Patients with X-linked hyper-IgM syndrome are unable to activate their B cells fully. Lymphoid tissues in patients with hyper-IgM syndrome are devoid of germinal centers (top panel), in comparison with a normal lymph node (bottom panel). B-cell activation by T cells is required both for isotype switching and for the formation of germinal centers, where extensive B-cell proliferation takes place. Patients with hyper-IgM syndrome have a mutation in the CD40 ligand gene, which lies on the X chromosome, and thus their T cells cannot fully activate their B cells. Only weak IgM responses are made to T-cell dependent antigens and serum immunoglobulin is predominantly IgM. Photographs courtesy of R Geha and A Perez-Atayde.

which cannot engage CD40; the B cells themselves are normal. We learned in Chapter 8 that CD40 ligand plays a critical role in the T-cell dependent activation of B-cell proliferation and these patients show that CD40 ligand is also essential for induction of the isotype switch and the formation of germinal centers (Fig. 10.11). The defects in cell-mediated immunity in these individuals may be due, at least in part, to the inability of their T cells to deliver an activating signal to macrophages by engaging the CD40 expressed on these cells (see Section 7-28). A defect in T-cell activation could also contribute to the profound immunodeficiency suffered by these patients, however, as studies on mice that lack CD40 ligand have revealed a failure of antigen-specific T cells to expand in response to primary immunization with antigen.

In XLA, the hunt for the cause of the disease led to a previously unidentified gene product. In the case of X-linked hyper-IgM syndrome, the gene for CD40 ligand was cloned independently and only then identified as the defective gene in this disorder. Thus, inherited immunodeficiencies can either lead us to new genes or help us to determine the roles of known genes in normal immune system function.

10-9 Defects in complement components cause defective humoral immune function and persistence of immune complexes.

Not surprisingly, the spectrum of infections associated with complement deficiencies overlaps substantially with that seen in patients with deficiencies in antibody production. Defects in the classical pathway and in C3 are associated with a wide range of pyogenic infections, emphasizing the important role of C4 and C3 as opsonins, promoting phagocytosis of bacteria (Fig. 10.12). In contrast, defects in the membrane-attack components of complement (C5–C9) have more limited effects and result exclusively in susceptibility to *Neisseria* spp. This indicates that host defense against these bacteria, which are capable of intracellular survival, is mediated by extracellular lysis by the membrane attack complex of complement.

The early components of the classical complement pathway are particularly critical for the elimination of immune complexes, which can cause significant pathology in autoimmune diseases such as systemic lupus erythematosus (see Chapter 12), and occasionally, in persistent infections. As we learned in Chapter 8, complement components attached to soluble immune complexes allow them to be transported, ingested, and degraded by cells bearing complement receptors. Transport is mediated by erythrocytes that capture immune complexes via the complement receptor CR1, which binds specifically to C4b and C3b. When this mechanism is inoperative, immune complexes are deposited in the tissues. Accumulating immune complexes activate phagocytes, causing inflammation and local tissue damage.

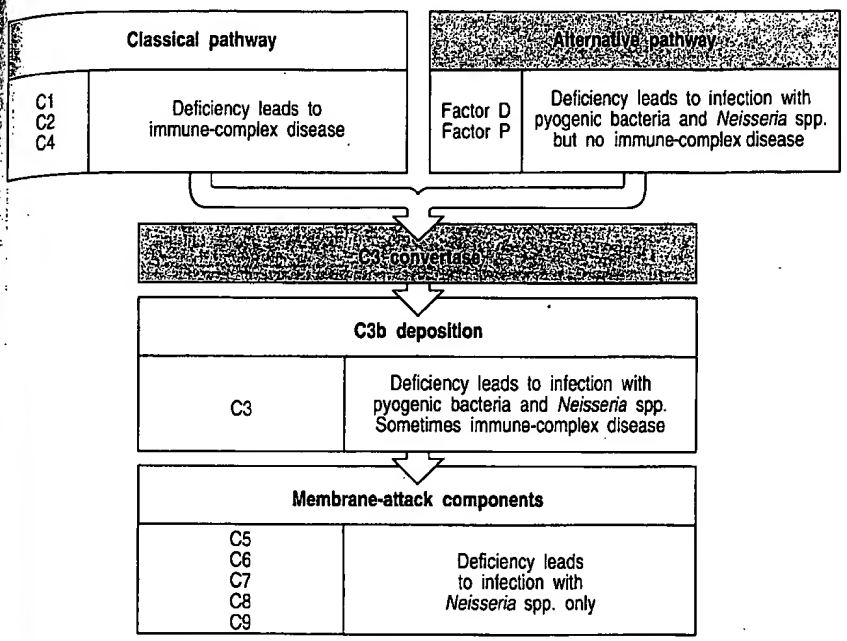

Fig. 10.12 Defects in complement components are associated with susceptibility to certain infections as well as accumulation of immune complexes. Defects in the early components of the alternative pathway lead to susceptibility to extracellular pathogens, and defects in the early components of the classical pathway affect removal of immune complexes via the complement receptor CR1, leading to immune complex disease. Finally, defects in the membrane-attack components are associated only with susceptibility to strains of *Neisseria* spp., the causative agents of meningitis and gonorrhea, implying that the effector pathway is important chiefly in defense against these organisms.

Deficiencies in control proteins that regulate complement activation can cause either immunodeficiency or autoimmune-like disease. People defective in properdin (factor P), which enhances the activity of the alternative pathway, have a heightened susceptibility to *Neisseria* spp. By contrast, patients lacking decay-accelerating factor (DAF) and CD59, which protect host cell surfaces from alternative pathway activation, destroy their own red blood cells. This results in the disease paroxysmal nocturnal hemoglobinuria, as we learned in Chapter 8. A more dramatic consequence arising from the loss of a regulatory protein is seen in patients with C1-inhibitor defects. These individuals fail to control the inappropriate activation of the classical pathway of complement activation and the uncontrolled cleavage of C2 allows the generation of a vasoactive fragment of C2a, causing fluid accumulation in the tissues and epiglottal swelling that may lead to suffocation. This syndrome is called **hereditary angioneurotic edema**.

10-10 Phagocytic cell defects permit widespread bacterial infections.

The leukocyte integrins CD11a/CD18 (LFA-1), CD11b/CD18 (MAC-1/CR3), and CD11c/CD18 (CR4/gp150,95) are important for phagocytic cell adhesion, migration across blood vessel walls, and ingestion of bacteria opsonized with complement fragments (see Section 7-2). If these integrins are defective, phagocytes cannot get to sites of infection to ingest and destroy pathogens. Deficiencies have been identified in the leukocyte integrin common β_2 subunit, CD18, which result in infections that are resistant to antibiotic treatment and persist despite an apparently effective cellular and humoral adaptive immune response. Neutropenia associated with chemotherapy, malignancy or aplastic anemia is associated with a similar spectrum of severe pyogenic bacterial infections.

Most of the other known defects in phagocytic cells affect their ability to kill intracellular and/or ingested extracellular bacteria (Fig. 10.13). In **chronic granulomatous disease**, phagocytes cannot produce the superoxide radical and their antibacterial activity is thereby seriously impaired. Several different genetic defects, affecting any one of the four constituent proteins of the NADPH oxidase system, can cause this. Patients

Type of defect/name of syndrome	Associated infectious or other diseases
Leukocyte adhesion (CD18) deficiency	Widespread pyogenic bacterial infections
Chronic granulomatous disease	Intra- and extra-cellular infection, granulomas
G6PD deficiency	Defective respiratory burst, chronic infection
Myeloperoxidase deficiency	Defective intracellular killing, chronic infection
Chediak-Higashi syndrome	Intra- and extra-cellular infection, granulomas

Fig. 10.13 Defects in phagocytic cells are associated with persistence of bacterial infection. Defects in the leukocyte integrins with a common β subunit (CD18) prevent phagocytic cell adhesion and migration to sites of infection. The respiratory burst is defective in chronic granulomatous disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency and myeloperoxidase deficiency. In chronic granulomatous disease, infections persist because macrophage activation is defective, leading to chronic stimulation of CD4 T cells and hence to granulomas. Vesicle fusion in phagocytes is defective in Chediak-Higashi syndrome. These diseases illustrate the critical role of phagocytes in removing and killing pathogenic bacteria.

with this disease have chronic bacterial infections, which, in some cases, lead to the formation of granulomas. Deficiencies in the enzymes glucose-6-phosphate dehydrogenase and myeloperoxidase also impair intracellular killing and lead to a similar, although less severe, phenotype. Finally, in **Chediak-Higashi syndrome**, an unknown defect causes a failure to fuse lysosomes properly with phagosomes; the cells in these patients have enlarged granules and impaired intracellular killing.

10-11 Defects in T-cell function result in severe combined immunodeficiencies.

Although patients with B-cell defects can deal with most pathogens adequately, patients with defects in T-cell development are highly susceptible to a broad range of infectious agents. This demonstrates the central role of T cells in adaptive immune responses to virtually all antigens. As such patients make neither specific T-cell dependent antibody responses nor cell-mediated immune responses, and thus cannot develop protective immunity, such defects are called **severe combined immune deficiency (SCID)**.

There are several different defects that lead to the SCID phenotype. In X-linked severe combined immune deficiency, T cells fail to develop because of a mutation in the common γ chain of several cytokine receptors, including those for the interleukins IL-2, IL-4, IL-7, IL-9, and IL-15. We will examine this defect further in Section 10-12. Two defects in enzymes involved in purine degradation, **adenosine deaminase (ADA) deficiency** and **purine nucleotide phosphorylase (PNP) deficiency**, also give rise to T-cell deficiencies and a SCID phenotype. Both defects result in an accumulation of nucleotide metabolites that are particularly toxic to developing T cells. B cells are also somewhat compromised in these patients.

Recently, the molecular basis of **Wiskott-Aldrich syndrome (WAS)**, a disease that affects not only B and T lymphocytes but also platelets, has begun to emerge. It is caused by a defective gene on the X chromosome, encoding a protein called WAS protein (WASP). This protein has been shown to bind Cdc42, a small GTP-binding protein that is known to regulate the organization of the cytoskeleton and to be important for the effective collaboration of T and B cells. The WAS protein also has the capability of binding SH_3 domains—protein domains found on some proteins of intracellular signaling pathways—and may take part in other signaling pathways. It is expressed in thymus, spleen, and certain tumors of hematopoietic origin and is likely to be a key regulator of lymphocyte and platelet development and function.

One class of SCID individuals lack expression of all MHC class II gene products on their cells. This condition is referred to as the **bare lymphocyte syndrome**. Since the thymus also lacks MHC class II molecules CD4 T cells cannot be positively selected and therefore few develop. The antigen-presenting cells in these individuals also lack MHC class II molecules and so the few CD4 T cells that develop cannot be stimulated by antigen. In these individuals, MHC class I expression is normal and CD8 T cells develop normally. However, they suffer severe combined immunodeficiency, illustrating the central importance of CD4 T cells in adaptive immunity to most pathogens. The syndrome is caused by mutations in one of several different genes that regulate MHC class II gene expression rather than in the MHC genes themselves. At least five complementing gene defects have been defined in patients who fail to express MHC class II molecules, which implies that at least five different genes are required for normal MHC class II gene expression. One of these, named the **class II transactivator**, or **CIITA**, is known to be responsible for some cases, while a protein that binds to the MHC class II promoters, called RFX, is defective in others. An understanding of the other genes that cause this defect is still being sought.

A family showing almost complete absence of cell-surface MHC class I molecules has been described. These patients have normal levels of mRNA encoding MHC class I molecules and normal production levels of MHC class I proteins. The defect was shown to be similar to that of the TAP mutant cells we learned about in Section 4-7 and indeed, affected members of this family had mutations in a TAP gene. These people are immunodeficient owing to a lack of CD8 T cells.

An interesting mutant mouse strain called *scid* (because it has a severe combined B- and T-cell immune deficiency) has a defect in the enzyme DNA-dependent kinase, which binds to the end of the double-stranded breaks that occur during the process of antigen receptor gene rearrangement. Many DNA hairpin structures, which are formed when DNA rearrangement is initiated, have been found in T-cell receptor δ-chain genes of immature thymocytes of *scid* mice, and cells from *scid* mice can be rescued by transfection with the catalytic subunit of DNA-dependent protein kinase. Thus, it seems likely that DNA-dependent kinase is involved in resolving the hairpin structure (see Fig. 3.21). Only rare VJ or VDJ joints are seen in *scid* B and T cells, and most of these have abnormal features. These mice therefore produce very few mature B and T cells. Recently, similar abnormal DJ joints have been observed in pre-B cells of some patients with autosomal severe combined immunodeficiency and cells of such patients, like those of *scid* mice, are abnormally sensitive to ionizing radiation. Other patients who appear to have mutations of *RAG-1* or *RAG-2* genes, also show a SCID phenotype.

In patients with **DiGeorge syndrome** the thymic epithelium fails to develop normally. Without the proper inductive environment T cells cannot mature, and both T-cell dependent antibody production and cell-mediated immunity are absent. Such patients have some serum immunoglobulin and variable numbers of B and T cells. The severe combined immunodeficiency diseases abundantly illustrate the central role of T cells in virtually all adaptive immune responses. In many cases B-cell development is normal, yet the response to nearly all pathogens is profoundly suppressed.

10-12 Defective T-cell signaling, cytokine production, or cytokine action can cause immunodeficiency.

As we learned in Chapter 7, virtually all adaptive immune responses require the activation of antigen-specific T lymphocytes and their differentiation

into cells that produce cytokines acting on specific cytokine receptors. Several gene defects have been described that interfere with these processes. Thus, patients who lack CD3γ chains have low levels of surface T-cell receptors and defective T-cell responses. Patients making low levels of mutant CD3ε chains are also deficient in T-cell activation. Patients who make a defective form of the cytosolic protein tyrosine kinase ZAP-70 (see Section 4-29) have more recently been described. Their CD4 T cells emerge from the thymus in normal numbers, whereas CD8 T cells are absent. However, the CD4 T cells that mature fail to respond to stimuli that normally activate via the T-cell receptor and the patients are thus very immunodeficient.

Another group of patients shows absence of IL-2 production upon receptor ligation, and these patients have a severe immunodeficiency; however, T-cell development is normal in these individuals, as it is in mice that have mutations in their IL-2 genes from gene knock-out (see Section 2-37). These IL-2-negative patients have heterogeneous defects; some of them fail to activate the transcription factor NF-AT (see Section 4-29), which induces transcription of several cytokine genes in addition to the IL-2 gene, and therefore presumably produce low levels of these cytokines as well. This may explain why their immunodeficiency is more profound than that of mice whose IL-2 gene has been disrupted; these mice can mount adaptive immune responses through an IL-2-independent pathway, possibly involving the cytokine IL-15, which shares many activities with IL-2. Nevertheless, mice lacking the ability to make IL-2 are susceptible to a variety of infectious agents.

There is an interesting contrast between patients deficient in IL-2 and those with X-linked severe combined immunodeficiency (X-linked SCID), which is caused by a defect in the γ chain of the IL-2 receptor. T cells in X-linked SCID patients fail to develop, while B cells appear reasonably normal. As mice and humans that lack IL-2 have normal T-cell development, the γ chain of the IL-2 receptor must be important in T-cell development for reasons unrelated to IL-2 binding or IL-2 responses. The recent demonstration that the IL-2 receptor γ chain is also part of other cytokine receptors, including the IL-7 receptor, may explain its role in early T-cell development. The γ chain appears to function in transducing the signal for this group of receptors and interacts with a kinase, JAK3 kinase, which has been shown to be defective in patients with an autosomally inherited immunodeficiency similar in phenotype to X-linked SCID.

As in all serious T-cell deficiencies, X-linked SCID patients do not make effective antibody responses to most antigens, although their B cells appear normal. However, since the gene defect is on the X chromosome, one can determine whether the lack of B-cell function is solely caused by the lack of T-cell help by examining X-chromosome inactivation (see Section 10-7) in B cells of unaffected carriers. Naive IgM-positive B cells have inactivated the defective X chromosome more often than the normal one, showing that B-cell development is affected by, but not wholly dependent on, the common γ chain. However, mature memory B cells that have switched to isotypes other than IgM, carry an inactive defective X chromosome in most cells. This may reflect the fact that the IL-2 receptor γ chain is also part of the IL-4 receptor. Thus, B cells that lack this chain will have defective IL-4 receptors and will not proliferate in T-cell dependent antibody responses. X-linked SCID is so severe that children who inherit it can survive only in a completely pathogen-free environment, unless given antibodies and successfully treated by bone-marrow engraftment. A famous case in Houston became known as the 'bubble baby' because of the plastic bubble in which he was enclosed to protect him from infection.

The production of defects in several cytokine and cytokine receptor genes in gene knock-out mice is rapidly increasing our understanding of the role of individual cytokines in immunity. Mice lacking transforming growth factor-β (TGF-β) die of overwhelming inflammatory disease, while mice lacking IFN-γ or the IFN-γ receptor succumb to infection with a range of intracellular pathogens, including *M. tuberculosis.* Several human families have recently been identified with children who are susceptible to early onset mycobacterial infections and have a homozygous deficiency of the IFN-γ receptor.

10-13 Bone marrow transplantation or gene therapy may be useful to correct genetic defects.

It is frequently possible to correct the defects in lymphocyte development that lead to the SCID phenotype by replacing the defective component, generally by bone marrow transplantation. The major difficulties in these therapies result from MHC polymorphism. To be useful, the graft must share some MHC alleles with the host. As we learned in Section 6-14, the MHC alleles expressed by the thymic epithelium determine which T cells can be positively selected. When bone marrow cells are used to restore immune function to individuals with a normal thymic stroma, both the T cells and the antigen-presenting cells are derived from the graft. Therefore, unless the graft shares at least some MHC alleles with the recipient, the T cells that are selected on host thymic epithelium cannot be activated by graft-derived antigen-presenting cells (Fig. 10.14).

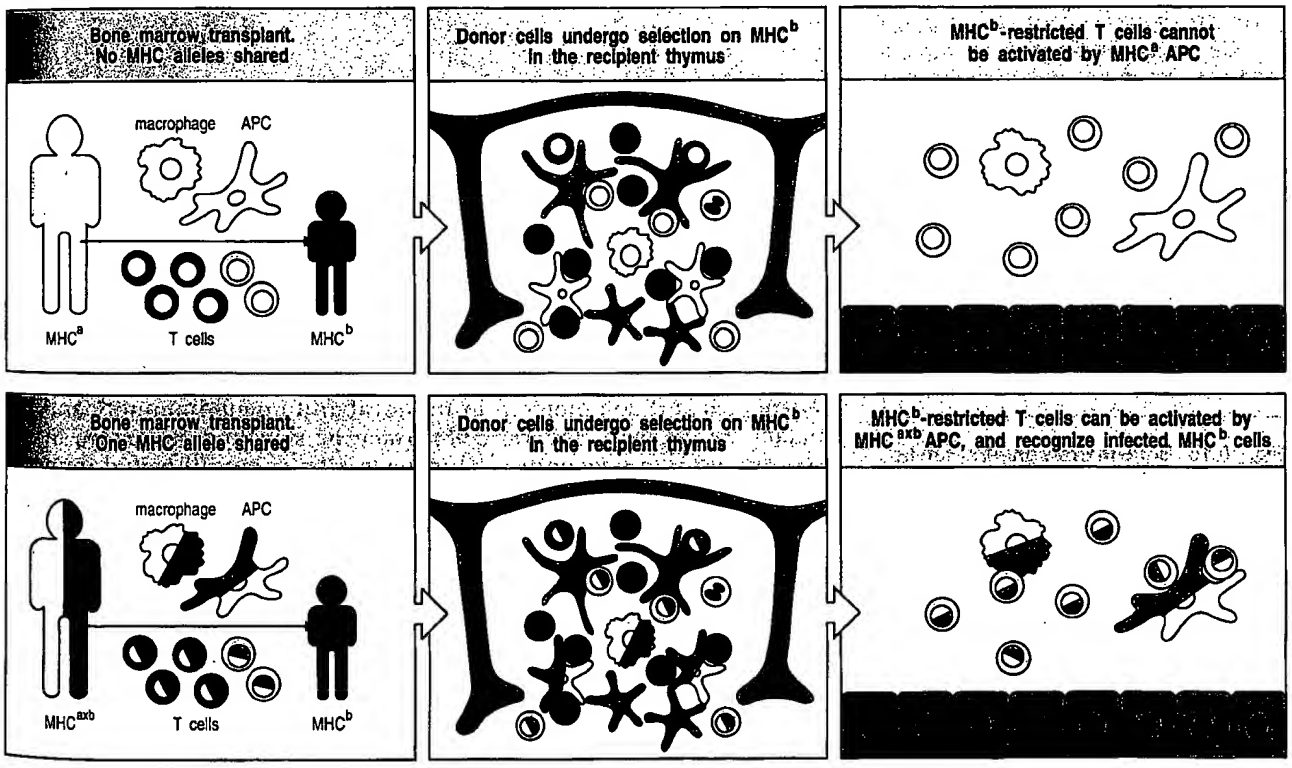

Fig. 10.14 Bone marrow donor and recipient must share at least some MHC molecules to restore immune function. If the bone marrow and the recipient thymus do not share any MHC alleles, T cells will mature in the thymus with receptors selected to recognize peptides presented by MHC molecules that are not expressed on the donor-derived antigen-presenting cells (APCs). These cells will not therefore be competent to mediate protective immunity (top panels). In the bottom panels, donor and recipient share the MHC^b allele, and T cells able to recognize MHC^b molecules are selected in the thymus. The antigen-presenting cells in the periphery can activate T cells that recognize MHC^b molecules; the activated T cells can then recognize infected MHC^b-bearing cells.

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